‘Quantum Biophysical Semeiotics Dyslipidaemic and Diabetic Constitutions’ “and” ‘Inherited Real Risk of CAD’

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ABSTRACT

Mit-DNA is mainly responsible for cell respiration in biological systems, and the genetic alteration of mit-DNA affects mitochondrial activity. It will be here analyzed a well defined mitochondrial cytopathy which is connected, from the moment of birth, with several inherited diseases, such as dyslipidaemia and diabetes. The chance to investigate, by mean of ‘Quantum Biophysical Semeiotics’ – QBS - indirectly, and through bed-side evaluation, mitochondria functionality opens new ways to understand and face the very beginning states of dyslipidaemia and diabetes, even potential, silent or not yet clinically diagnosed, and of the ‘Inherited Real Risk’ of Coronary Artery Disease (CAD), giving original impulses to diagnosis and primary prevention.

1. Introduction

A part from its inflammatory, infectious, degenerative, metabolic, neoplastic nature, a disease arises and evolves in relation to the individual constitution, since *environmental* factor, surely important, interacts with *genetic* factor always present, as clinical evidence shows it. As extreme example, let us consider the “traumatic” pathology: if the diseased subject does not die, of course, fracture evolves and ends in relation to patient constitution. In fact, there are notoriously identical cases, as concerns the initial severity, among them some people rapidly and completely recover, while other undergo morbidity and even mortality, due to complications, clearly in relation to efficacious tissue repair, bone synthesis, tissue heal, all events *genetically* directed. The primary role played by the constitution is manifest also in infectious diseases, including the common children diseases, viral in origin, which evolve especially, although not exclusively, in relation to psycho-physical situation of every individual and certainly to sensitivity to treatment, although nowadays only specific vaccines are successful.

The *constitutional factor* shows its primary role in degenerative well as metabolic diseases, in chronic inflammations, in connectivitis, and malignancies, as we demonstrated previously. There is nowadays a general agreement with the fact that "*genotype*" influences both the onset and the course of most common and frequent human diseases, very often associated with *environmental* factors, since it is plain that "without rice-field the rice does not grow" - Oncological Terrain [14]. To summarize, a part from its inflammatory, infectious, degenerative, metabolic, rheumatic, neoplastic nature, a disease arises and evolves in relation to the individual constitution, since *environmental* factor, surely determinative, must react with the *genetic* factor, which is always present. QBS enlarging enormously the borderland, really limited, of traditional, orthodox, physical semeiotics, allowed us, over the last decades, to precisely define a lot of constitutions [13]. In characterising QBS constitutions, it has been started from the hypothesis or conjecture – then revealed truth, scientifically speaking – that "altered" genome, nuclear as well as mitochondrial, modifies both function-structure of various parenchyma and function-structure of related microvessels, thus, permitting us to enlarge and complete Tischendorf's concept of Angiobiotopie [16]. Finally, by means of the original physical semeiotics, which proved to be essential and precious in giving rise to *Clinical Microangiology* [17], doctor now is able to recognize at the bed-side functional-structural modifications of tissue-microvascular-units, characteristic of the diverse constitutions, starting from two first decades of individual life, mainly as a consequence of alteration of glucosamine-glycanes of extra-cellular matrix, slowly evolving and worsening, if not recognized and treated.

This paper highlights the central role of mitochondria and mitochondrial DNA (mit- DNA) in the process that underlies the metabolic disorders and microcirculatory alterations, pre-pathological conditions of dyslipidemia. For this purpose it is useful the Quantum Biophysical Semeiotics - QBS, extension of the classical semiotics with the support of quantum and complexity theories, a scientific approach first described by Stagnaro [16] based on the Congenital Acidosic Enzymo-Metabolic Histangiopathy – CAEMH [2, 4, 5, 6], a unique mitochondrial cytopathy, present at birth and subject to medical therapy. According to the research of Stagnaro, today the doctors should be able to evaluate at the bedside of their patients, simply using the stethoscope [14], mitochondria functionality, as well as the functionality of all biological systems. For example, it is now possible, from the moment of birth, to make a diagnosis in order to detect the presence of 'Inherited Real Risk' of 'Type 2 Diabetes Mellitus' - T2DM linked with 'Diabetics and Dyslipidemic Constitution' [3], so that an intelligent prevention strategy can be implemented only on those subjects with 'Inherited Real Risk', even latent, without incurring additional costs for the NHS [18]. The prevention done on the basis of QBS constitutions - i.e. Coronary Artery Disease – CAD [1, 18], Oncological Terrain [2, 14], Diabetics Constitution [3, 13], etc. - will prevent the onset of the more serious diseases that humans suffer from today - for example, cancer, diabetes, ischemic heart diseases, including myocardial infarction. Blood glucose is obviously absorbed also by lever as well as adipose tissue, whose insulin receptors show an abnormal sensitivity to hormone in a highly differentiated manner: lever cell insulin receptors are typically well-functioning in QBS 'Lithyiasic Constitution'! [13] This action of insulin is regulated by genetic factors, environmental factors, blood-flow, circulating substances, and insulin signaling pathways [19]. Notoriously, a large number of diseases are associated with hyper insulinemia-insulin-resistance - IIR, such as obesity, particularly the visceral type, where one observes a direct link between insulin resistance, non insulin-dependent diabetes - T2DM, dyslipidemia, and arterial hypertension [3]. In addition, numerous substances from fat tissue appear to suppress insulin-mediated glucose up-take, including free fatty acids, tumor necrosis factor-alpha (TNF-a) and possibly leptons [20]. Infusion of these factors into normal animals suppresses insulin-mediated glucose up-take [21, 22].

According with the work of Stagnaro [3], insulin resistance and insulin-secretion derangement are correlated in a stable manner and both play a pivotal role in the onset of T2DM, always observed when interstitial fundamental matrix appears modified, as above- referred. In fact, i.e., insulin-secretion is physiologically ruled by insulinemia, by means of a feed-back mechanism, through insulin-receptors localized on the membrane of insular b-cell, whose modified "pericapillary sheet" is enlarged due to amyloid deposit, hindering local transit: the two factors are strictly related each other at large number of different levels [15].

In the onset of T2DM is crucial this modification of the fundamental substance Interstitial - "pericapillary sheet" - where GAGs [15] are modified in their relationships, because they are modified in their relationship. In fact, they are formed by cells (fibroblasts, mega-karyocytes, pericytes, myoblasts), whose n-DNA and mit-DNA and DNA is in turn genetically altered. Consequently, we observe the pathological function of GAGs in vasomotion [1] not only of the capillaries but also of small arteries and arterial by Hammersen [23] in the transit of various substances, including insulin, in the connection with water (water-bound), in the local biochemistry: this is the so defined 'Second Stage of the Natural History of T2DM'.

Due to these reasons the clinical on-set of T2DM appears later, because insulin-resistance in liver, adipose cells of the abdomen wall and skeletal muscles during the initial stage, i.e., for years or decades, may be balanced by increasing of the insulin secretion. Opie [24] described the "hyaline degeneration" of the Langherans pancreatic islets of hyperglycaemic patients, suggesting a possible relation to DM, although in that period amyloid protein was not yet identified as product of insular origin. In 1986, the protein secreted by b-cells was identifies and termed insular polypeptide amyloid [25]. Amyloid protein is composed by dense, interlacing fibrillae, which are colored by red and are birefrigent to polarized light. These fibrillae are formed by 20 proteins and a large number of them are considered related to specific diseases. Insular amyloid is present in 90 % of diabetic (T2DM) patients [26], composed of normal proteins, as component of serum P amyloid, and proteoglycans of heparansulfate type, present in both serum and healthy tissues.

The serum P protein component, related to acute phase proteins, may be associated to all amyloid fibrillae, which therefore are protected against proteolysis. In addition, experimental evidence shows the importance of this protein in case of amyloidosis "in vivo": in gene *knocked-out* rats the systemic amyloidosis on-set is later and its severity is less intense. Insular amyloidosis is related to the loss of approximately 40 - 50% of b-insular tissue. Human insular amyloid polypeptides bring about cytotoxity by a large number of pathological mechanisms, producing amyloid fibrillae. In addition, they undergo to glycation process. Hyperglycemia causes the production of amyloid both increasing the production of insular amyloid polypeptides and augmenting their fibrillopoietic properties [26]. According with QBS, doctors are able now-a-days to assess such as interstitial modification in an awful number of methods, different in difficulty. For instance, pancreas "in toto" urethral reflex informs on interstitial size, as well as the modified interstitial fundamental matrix, illustrated above in the initial stage of diabetes, slow significantly both local vasomotility and vasomotion [1, 3].

It is generally admitted that the T2DM may occur at least 12 years before the clinical diagnosis is made, and retinopathy can develop at least 7 years before the diagnosis. During the time that diabetes is undiagnosed and untreated, complications, that could be avoided, are developing. Therefore, early diagnosis should be established to avoid those complications. In fact, in order to prevent well known diabetic complications, it is extremely necessary that the doctors could use a "clinical" tool reliable in diagnosing early diabetes mellitus, i.e., "since its initial stages" [3]. Until now, unfortunately, diabetes mellitus is too often diagnosed accidentally, i.e., by occasional urinary or blood tests. Furthermore, epidemiologic studies indicate that 50% of individuals with 2-hour post glucose challenge values over 200 mg/dL, a value diagnostic for diabetes, were not

previously diagnosed as being diabetic [27]. T2DM is now widely considered to be one component within a group of disorders called the metabolic syndrome3, both classic and "variant" [3]. Such as syndrome, also known formerly as dys-metabolic syndrome X, is formed by some characteristic factors: abdominal obesity, atherogenic dyslipidemia (elevated triglyceride [TG] levels, small low-density lipoprotein [LDL] particles, low high-density lipoprotein cholesterol [HDL-C] levels), elevated blood pressure, insulin resistance (with or without glucose intolerance), and pro-thrombotic and pro-inflammatory states. According to Stagnaro [13], genome's information are transmitted simultaneously both to parenchyma and related micro-vessels, so that mutations in parenchymal cell n-DNA and mit-DNA are the *conditio sine qua non* of the most common human disorders, like diabetes, CAD, and cancer, today's epidemics.

In fact, all these diseases are based on a particular congenital, functional, mitochondrial cytopathy, mostly transmitted through mother, and defined Congenital Acidosic Enzyme-Metabolic Histangiopathy, CAEMH [2]. The contribution of these modifications to the relative pattern of diabetic syndrome, based always on genetic or inborn errors – CAEMH - is different from patient to patient and during the disorder's evolution. For instance, in case of diabetic syndrome, insulin-secretion increases silently for years or decades, before appearing, i.e., of dyslipidemia and/or T2DM. This is a pre-clinical stage that is not detectable through usual clinical tests, so it needs to explore new approaches, such as that introduced QBS [3, 13] which through bed-side evaluation, can assess the existence of pre-metabolic syndrome, that can last for years or decades, pre-clinical stage of the disease still potential or on training (evolution to pathology, pre- morbid state or gray area), so allowing an effective prevention.

In addition, parenchymal gene mutations cause local microcirculatory remodeling, so doctor can evaluate it at the bedside in a reliable manner, gathering indirect information on inherited modifications of relative parenchymal cell, since biological system functional modifications parallel gene mutation, according to Angiobiopathy theory [14, 16, 17]. The presence of intense CAEMH – termed CAEMH-α - in a well-defined area, i.e., pancreas, involved by gene mutations in both n-DNA and mit-DNA, is the ground for one or more QBS constitutions [13] which could brings about their respective congenital Real Risks - RR [18] characterized by microcirculatory remodeling from biophysical-semeiotic viewpoint, especially intense under environmental risk factors. Such as congenital micro-vascular remodeling, shows since birth interesting structures, i.e., newborn-pathological, type I, subtype b), Endoarteriolar Blocking Devices, EBD, localized in small arteries, according to Hammersen [23]. As a consequence of above, briefly referred remarks, physicians are able nowadays to demonstrate the presence of typical pathological EBD in well defined micro-vessels, which play a central role, i.e., in dyslipidemic 'Inherited Real Risk'.

Notoriously, T2DM and obesity, major health problems worldwide, are considered to be closely related [3]. In fact, T2DM can involve exclusively individuals with both dyslipidemic and diabetic constitutions [3, 13, 14, 16, 17, 18], because the accumulation of triglycerides an cholesterol in cells lets less sensitive to the hormone the local insulin receptors of muscle cells, but also those of adipose tissue, especially visceral. Therefore, there is an increased insulin production in pancreatic islets, which functionally collapse to T2DM, after a period of insulin hypersecretion, in the case of inherited real risk of diabetes depending on diabetics constitution. If there is just diabetics constitution, but associated with autoimmune rheumatic constitution, there may happen only T1DM. Furthermore, diabetic and dyslipidaemic constitutions could be responsible of Coronary Artery Disease – CAD inherited real risk [1].

Nuclear Peroximose Proliferator-Activated Receptors - PPARs [28] play a pivotal role in the development of metabolic syndrome, T2DM, and in many cardiovascular disorders is certainly of paramount importance, but according with Stagnaro [3], we have to consider the existence of both QBS diabetic and dyslipidaemic constitutions, *conditio sine qua non* of both metabolic

syndrome (classic and “variant”) and the most severe human diseases. It is now well known that treating metabolic syndrome can prevent or ameliorate cardiovascular disease and T2DM [29]. The metabolic syndrome is a highly prevalent clinical entity, so obesity, PPARs modulation and insulin resistance are the central components of this complex syndrome, and diet and physical exercise can prevent a large number of DM [30]. However, all these events can occur only in individuals with diabetic as well as dyslipidemic constitutions that represent the first stage in the development of all disorders at the base of metabolic syndrome [16].

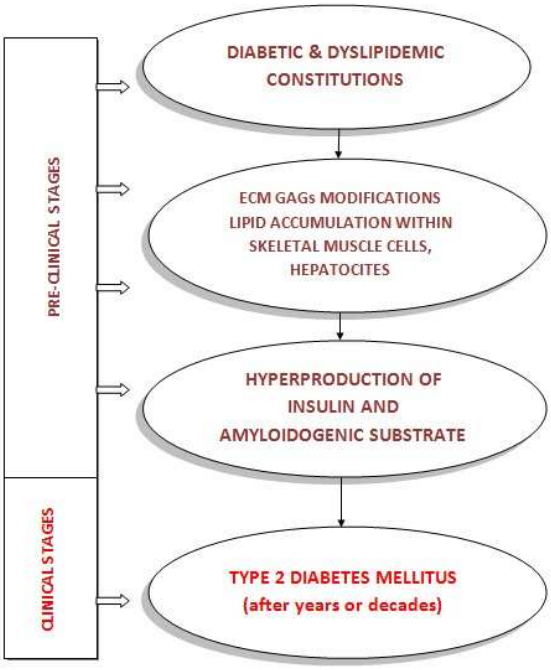
As regards the essential fact that the fall in insulin secretion, leading to hyperglycemia, separates patients with metabolic syndrome in two groups, *with* or *without* overt diabetes, we have to pay attention to the presence of the above-mentioned QBS constitutions, associated or isolated, which enlighten the real reason of the different events. In fact, the fall in insulin secretion can occur exclusively in patients involved by both constitutions.

Patients with IIR are “at Real Risk” for both CAD [1, 3], and a lot of others metabolic disorders, including T2DM, as allows us to state a long clinical and experimental evidence, i.e., acute myocardial infarct at the age of 70 years, occurred in the absolute absence of well-known risk factors, generally admitted by all authors, but on the base of “diabetic, dyslipidemic, hypertensive, Oncological QBS constitutions” and IIR, however, properly controlled by diet, etymologically speaking. The increased risk is related to the association of diverse factors with hyper insulinemia-insulin-resistance - IIR syndrome (classic and “variant” metabolic syndrome), although IIR for itself can increases the risk for CAD. In fact, four large prospective studies have demonstrated that hyper insulinemia is an independent risk factor for CAD in Caucasian males; however, similar finding have not been demonstrated in women and have not been addressed in other ethnic groups [31, 32]. According with Stagnaro [3] clinical researches, we must go “beyond hyper insulinemia-insulin-resistance” to comprehend better the onset of both cardiovascular disease and T2DM, unavoidable condition for a successful primary prevention of a large number of metabolic disorders [33, 34]. Accurate study of EBD in general, and those of coronary artery in particular, now-a-days possible “at the bed-side” by the aid of QBS, and the different QBS constitutions have opened new and promising ways in primary prevention and in a better comprehension of both arteriosclerosis, including CAD, and T2DM. Stagnaro clinical researches enlighten the intriguing P. Hayden’s [35] theories, and he completely agrees with him: “What is even more interesting is the possibility that T2DM may be a vascular disease with a common genetic abnormality located in the endothelial nitric oxide gene (eNOS) itself, common to both T2DM and Cardiovascular disease” (personal communication).

Furthermore, as regards to the diagnosis of inherited real risk of T2DM, from the moment of birth there is the presence of diabetic constitution, always associated with dyslipidemic constitution, independently of raised lipid blood level in subsequent time. Later on, through QBS we can observe a second stage, characterized by lipid accumulation within skeletal muscle cell, hepatocites, i.e., classical and “variant” metabolic syndrome, where there is not lipid accumulation in hepatocytes [36], and in pancreatic cells, and local insulin resistance occurs. Under such pathological conditions, the pancreas produces more insulin and the amyloidogenic substrate amylin resulting in islet amyloid formation, according to P. Hayden [37, 38].

In fact, at this point, from QBS view-point, Langheran’s islets interstitium appears clearly increased in size, due to islet amyloid deposit: pancreatic-“in toto” urethral reflex is augmented in a clear-cut way, preceding and accompanying T2DM19.

Finally, after years or decades, in the III Stage of Natural History of Diabetes, according to Stagnaro [15] as a consequence of insulin secretion failure, T2DM occurs, according to Scheme 1.



Scheme 1

Scheme 1 shows that in case of 'Inherited Real Risk' of diabetes, diabetic constitution is always associated with dyslipidemic constitution, which brings together to a lipid accumulation within skeletal muscle cell, hepatocites (absent in 'variant' form of metabolic syndrome), independently of raised lipid blood level, and later on to hyper-production of both insulin as well as amyloidogenic substrate of amylin, i.e., metabolic syndrome, classic or 'variant', and only after years or decades to T2DM. Through the objective QBS examination in a few minutes, it is possible to recognize and quantify if a patient has got any QBS constitution and congenital Real Risk (RR) to have a disease by mean the observation of EBD, type I, subtype a) cancerogenous b) nonspecific. The EBD is a kind of dam which opening or closing itself regulates blood flow in micro-vessels directed to the parenchyma. With a simple stethoscope it is detectable if there is a clear genetic predisposition to have a disease such as cancer, diabetes or CAD, and it is possible to quantify and monitor it over time since birth. So there is the possibility of implementing a prevention on a huge hall in individuals clinically finally selected in a rational way. This new way of prevention will not allow to materialize physical illness, which can be anyway potentially present (or be RR as "residual") at potential level. As similarity we can think of butterfly valves that regulate the flow and mixture of air and gasoline in car engines, since the EBD are dams that are simply regulating blood flow to the parenchyma, precisely cells of various tissues. If these DEB are tough, rigid, inelastic, there is RR. There are EBD Type I - located in small arteries, according to Hammersen – and Type II – they can be found in the arterioles that are, according to Hammersen, between small arteries and capillaries: only type II is ubiquitous, in the sense that it is observed everywhere, in all arteries. Even these physiological types get sick or old. However, the other types, pathological-new-formed, are expressions of the RR, of potential disease, they occlude more, but through therapy they can be transformed from the subtype a) tumoral, to subtype b) a-specific, and then in "physiological" type, decreasing gradually their amount.

2. QBS diagnosis of dyslipidemia

Clinical evidence demonstrates that the dyslipidaemic constitution necessarily exists: among individuals comparable as far as age, sex, social state, lifestyle, diet, and so on, are concerned, some are dyslipidaemic, while other are not. In addition, among children of dyslipidaemic parents only some show high cholesterol concentration (total Ch. and/or LDL and/or non-HDL) as well as triglycerides, of course, when diet, etymologically speaking, i.e. day program, is the same.
Finally, among individual with identical lipidaemic concentrations values, the seriousness of well-known disorders are clearly different. Therefore, the "real" risk of dyslipidaemia, based on *genetic* alterations, truly exists, as allows to state clinical evidence, beyond actual genetic investigations. In a few minutes, QBS permits doctor to recognize, at the bed-side and in "quantitative" manner, both the presence of dyslipidaemic constitution and dysplipidaemia, by a large number of methods, which obviously need a very different knowledge of this original semeiotics. As follows, in the interest of reader not jet experienced in this diagnostic method, we will illustrate two ways, easy enough to perform, certainly reliable in recognizing dyslipidaemic situations, even in initial stages, until now undiagnosed clinically.

Microcircular Functional Reserve

Alterations of mit-DNA and n-DNA cause CAEMH in parenchymal area, a parenchymal gene mutation that induces, in case of intense CAEMH, a local microcirculatory remodeling (LMR), a congenital micro-vascular remodeling possible to evaluate and investigate getting information about parenchymal cells through several QBS signs and behavior. For instance, through the observation of EBD and their structure and functioning on pancreatic micro-vessels we can study the LMR and investigate if there is T2DM or inherited real risk of diabetes and endothelial dysfunctions. A lowering microcirculatory blood flow induces a LMR due to EBD type 1 subtype b), a-specific, synonymous of reduced tissue oxygenation. Through QBS we can measure and evaluate the Microcirculatory Functional Reserve (MFR) activity of related micro-vessels. MFR is correlated with microcirculatory bed or Tissue Micro-vascular Unit (T.M.U.) and is possible to evaluate it through the observation of pancreatic oxygenation, pancreatic pH, T.M.U. structure and function, local metabolic situation, pancreatic preconditioning and EBD investigation.

The adipose tissue-gastric aspecific reflex

A) Preconditioning of abdominal adipose tissue

In order to apply the QBS method in bed-side diagnosis of diabetes mellitus and dyslipidemia, doctor has *at least* to know auscultatory percussion of the stomach. Of course, for the accurate and exhaustive application of Quantum Biophysical Semeiotics, complete and safe knowledge of this method are required. Auscultatory percussion of the stomach, essential in QBS, is performed as follows: in an individual in supine position and psycho-physically relaxed, placed correctly the bell piece of the stethoscope upon skin projection area of the interested parenchyma, i.e. the stomach or the precordium – as indicated in Figure 1 – doctor applies *directly and gently* digital percussion with the pulp of middle finger, two times subsequently on the same

point along radial, centripetal lines, starting a little far from the bell-piece of the stethoscope, moving thereafter towards it.

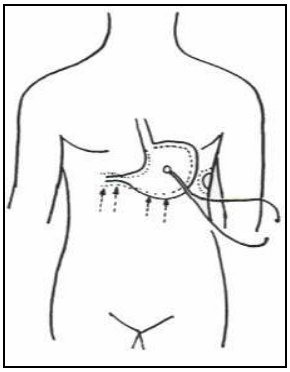


Figure 1

Figure 1 shows both the precise location of bell-piece of stethoscope and parallel and centripetal lines, on which digital percussion, directly and gently, must be applied in order to outlining properly the great curvature of stomach, or in practice only a small tract. Notoriously there is a great structural-functional difference between "central" adipose tissue, i.e., abdominal and visceral adipose tissue, and the "peripheral" one, i.e., thigh. Insulin-resistance involves, as clinically demonstrated by QBS, almost always the central adipose tissue, which has been investigated, but not the peripheral adipose tissue, i.e., tight. QBS preconditioning is the method of examination based on comparison of the parameters values of some reflexes, assessed in "quantitative" manner at rest (basal line) and then in a second evaluation, performed after a pause of exactly 5 seconds from the first one. From the technical clinical-micro-angiological point of view, by means of this clinical tool, doctors can evaluate precisely both structure and function of local micro-vascular system, i.e., local Microcirculatory Functional Reserve (MFR) [7, 8]. From technical view-point, it is necessary to know the 'Auscultatory Percussion of Stomach' [16].

In an individual, psycho-physically relaxed and in supine position, cutaneous "lasting" pinching of the abdomen (lateral abdominal part at right and at left, or near to umbilicus) physiologically provokes gastric aspecific reflex (Fig. 1: in the stomach, both fundus and body are dilated, while antral-pyloric region contracts) after latency time (lt) 8 seconds [1, 2, 3]. In health, immediately after preconditioning lt rises to $\geq$ 16 seconds, double value. On the contrary, in subjects with dyslipidaemic constitution as well as obviously in dyslipidaemic patients, latency time at basal line results $\leq$ 8 seconds and after *preconditioning* appears to be either slightly raised in no statistically manner, i.e., 10 seconds, or the same, if not reduced, in inverse relation to the seriousness of underlying disorder. Without discussing patho-physiological mechanisms, the values of gastric aspecific reflex parameters are based on, it is enough to know that these behaviors are related to local Microcirculatory Functional Reserve (MFR), which in turn is strictly related to both anatomy and function of important microcirculatory structures, essential in direct capillary blood-flow, which parallel parenchymal alteration, both structural and functional. Among these really interesting structures we consider, later, only ubiquitarious Endoarteriolar Blocking Devices (EDB). According to Stagnaro research [17], in fact, altered "genetic" information acts on both parenchymal function-structure and local micro-vessels, that nowadays can be assessed clinically, thanks to QBS, which originated Clinical Microangiology. Interestingly, the "intense" stimulation of adipose tissue trigger points, by pinching of lateral abdominal quadrant, allows doctor to exclude or recognize in only one second the dyslipidaemic constitution. In health, under the above

illustrated experimental condition, adipose tissue trigger points “intense” stimulation does not bring about *simultaneously* the aspecific gastric reflex. On the contrary, the reflex appears *simultaneously*, showing an intensity less than 1 cm, in presence of the dyslipidaemic constitution.

B) Evaluation of the EBD of “central” adipose tissue

EBD, present in all tissues, are manifold microvascular structures, made up by smooth muscle cells, placed in different ways, and lined with endothelial cells. They are localized in two stations (first and second stations) along small arteries, according to Bucciante whose media is formed by two or more layers of smooth muscle cells [9, 10, 11].
Their action mechanism (blood-flow direction toward the capillary bed) is obvious, in that their contraction brings about volume reduction, while the relaxation causes arteriolar lumen obstruction, evaluated as dilation of mean urethral tract. EBD Clinical QBS evaluation represents practically the assessment of “mean” urethral reflex (dilation of urethral mean third), caused by cutaneous-sub-cutaneous lasting pinching, of average intensity of adipose tissue, we want to examine. In the figure the correct locations of the bell-piece of stethoscope and the lines upon which auscultatory percussion, directly and gently, must be applied, in order to out-lining properly both kidneys and urethras, are clearly indicated. After lt 3-4 seconds, appears the dilation (1 cm) of mean urethral third or mean urethral reflex, which in healthy lasts for 20 seconds exactly and, then, disappears for exact 6 seconds. Interestingly, *preconditioning* lengthens opening duration, which rises to about 22 seconds, while reduces closure duration, that lowers to ≤ 5 seconds, in relation to the degree or severity of underlying metabolic disorder. On the contrary, in case of dyslipidaemic constitution as well as dyslipidaemia, of course reflex duration (EBD opening) results ≤ 19 sec. (Normal value is NN = 20 seconds), and its disappearing persists for 6-7 seconds (NN = 6 seconds exactly).

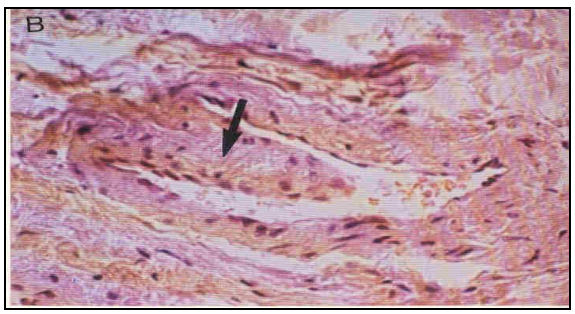


Figure 2

Figure 2 (published for kind permission of S.B. Curri) shows, in a very refined manner, a typical EDB with large installation base. It shows, in a very refined manner, a typical EDB with large installation base [39]. Moreover, soon after preconditioning these values either are unchanged, i.e. identical to those at basal line, or EBD opening appears to be lessened in a statistically significant manner, and the EBD closure is greater than before (7-8 seconds), in relation once again to the seriousness of underlying lipidic dysmetabolism. In conclusion, the precise evaluation of microcirculation on “central” adipose tissue allows, in really easy way, to assess local MFR and, then, to recognize the dyslipidaemic constitution, starting from the first decades of life. A large variety of further biophysical-semeiotic evaluations, which require a steady knowledge of the new physical

semeiotics, permits doctor to gather a lot of information about local metabolic situation and consequently about responsiveness to various hormons, including insulin [12,13].

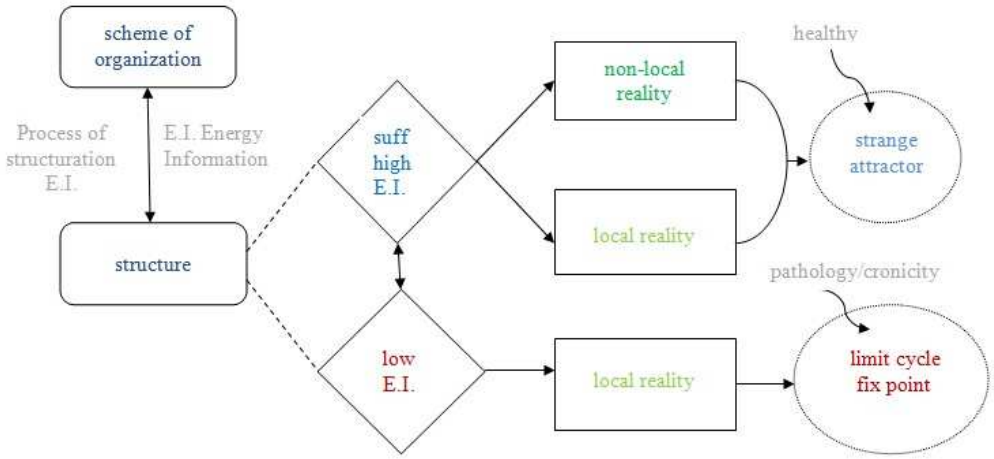
3. Dyslipidemia and Type 2 Diabetes Mellitus: prevention and therapy

Given the accumulating evidence that dyslipidaemia and diabetes mellitus, whether silent or not, carries a poor prognosis in patients with known diabetes, it is justified to follow an active policy even in patients who are totally free of symptoms. Essentially, the rationale for the use of histangio-protective drugs (like Cellfood, L-Carnitine, Co Q10, Conjugated-Melatonin, and so on) in patients with dyslipidaemia and/or T2DM clinically silent, relates three premises: the favorable effects of these products on lipid and glucose metabolism, the positive influence of these drugs on pancreatic preconditioning (for T2DM), because they improve blood flow in pancreatic tissue microcirculatory units, and the improvement of pancreatic microcirculatory remodeling, i.e., lowering the number of newborn-pathological type I, subtype b) EBD, when histangio-protective drugs are utilized in early stage, in fact the intensity of specific middle urethral reflex significantly decreases under such treatment. Practically, in order to ascertain clinically silent T2DM it is advisable to assess shape and intensity of low urethral reflex oscillations.

As far as pancreatic preconditioning is concerned, it is sufficient and hence advisable in day-to-day practice to assess the latency time of the second P.A.G.R. (Pancreatic Aspecific Gastric Reflex), i.e., in the second evaluation, performed exactly after a pause of 5 seconds from the end of the basal evaluation. In health, latency time raises in a significant manner from 12 seconds (basal value) to 24 seconds, i.e., to doubly value. From the practical viewpoint, both duration (Normal value is NN < 4 seconds) and differential Lt, i.e., disappearing time (3 < NN < 4), of pancreatic-caecum and/or -aspecific gastric reflex, i.e. fractal Dimension [3, 7], gives exhaustive information about pancreatic vessels morphological and structural situation, according to Angiobiopathy theory [14, 17].

Actually, important data are easily obtained also by means of the latency time of pancreatic caecum and/or -aspecific gastric reflex, which informs about pancreatic oxygen supply. In health, during digital “mean” pressure upon cutaneous projection area of the pancreas, basal latency time value is 12 seconds. However, doctor must remember that in case of T2DM ‘Real Risk’ and T2DM initial stage, such as parameter value is almost normal (less than 12 seconds), but reflex lasts 4 seconds or more (NN < 4 seconds), indicating diabetics pathological condition.

Analogously to the referred maneuver, concerning bedside quick diagnosing the dyslipidemic constitution, “intense” stimulation of pancreatic trigger points by mean of pinching, in health, does not cause gastric aspecific reflex. On the contrary, such as reflex appears *simultaneously*, under identical experimental condition, showing an intensity less than 1 cm, in presence of the diabetic constitution. In conclusion, in a long, well-established, clinical experience, the above-described QBS methods proved to be reliable, easy to perform on very large scale, useful, and suitable for detecting T2DM, even clinically silent or really initial, i.e. since inherited real risk of diabetes. In absence of ‘Inherited Real Risk’ of diabetes (Scheme 2), all diabetes risks factors will be mere spectators, because that person will never be affected by type T2DM: pathologies and chronicity of this kind will never happen. Scheme 2 shows that in human bodies there is physiologically the healthy coexistence of two different realities: local reality and non-local reality.



Scheme 2

The non-locality disappears if the mitochondrial respiratory activity and consequently EI – a catalytic subtle energy - sensitivity decreases. For example Lory's experiment [1, 2, 3, 16] fails, if is applied a stimulation in a subject following the apnea test, with the result of an impaired mitochondrial activity. The compensation takes place because of nuisances involving dissipative structural changes, but always subject to the power system's inherent conservative autopoietic organization.

The congenital QBS Real Risk (RR) arises at an intermediate stage between the scheme of organization and the structure, a first structuration from the scheme (not observable) on which we can identify it (in case there was) using simple clinical tests at bed-side, in a vision in which if there were RR, it would be able to tend to a pathology (potential disease), a pathology which, if occurred, would amount to a fully structuration of the scheme of organization (i.e., genetic alteration of mit-DNA) to disease. RR, if pathologically evolving, is the slow 'eventing' of disease events. Also considered in itself, whether static, is a manifestation of the structuring process of the organization. The process is reversible in the sense that through histangio-protective drugs like Cellfood, L-Carnitine, Co Q10 and melatonin-conjugated37, application of energy (i.e., NIR-LED), proper diet understood in the etymological sense, etc. the RR can become "residual", so that will not disappear nor will evolve towards the structure. The principle of the process is the Energy-Information - EI - catalytically nature, according to Manzelli [1, 2, 3]. The level of Vibration-Energy - EV, energy related to energy information - EI - from the perspective of QBS is measured on the level of tissue oxygenation: namely the lt of reflex. Indeed, stimulating the trigger - points in a biological system, such as the liver, "simultaneously" there is built up a simpatico-hyper-tonicity after a latency dependent on the intensity of the stimulus - related to the intensity of liberation in the biological system of adrenaline and nor-adrenaline – we observe the nonspecific gastric reflection - stomach swells - "simultaneously" to reach the critical level of low energy or low oxygen. Under these conditions, in fact the biological system has become thermodynamically isolated. We are in this case, in the non-local reality: there is simultaneity and synchronicity. On a completely healthy human being (without RR) EI is in fact high enough, and then there is simultaneity of information. Local and non-local reality co-exist, exist simultaneously but in parallel, they do not overlap. When EI decreases, EM –Energy Matter – as a consequence increases, and whether EI falls below a certain threshold, non-local reality "disappears" and we can observe just local reality. In summary, if there is enough high EI, there is not RR, while if there

is low EI, non transitory and not occasional - low EI in transient form, for instance, is with the apnea test in individuals completely healthy without RR – since permanent, then there is inherited RR of diabetes (associated, i.e., with diabetics and dyslipidaemic constitutions). The production of EI may be endogenous - it is created endogenously in humans through a transformation of breath in subtle and vital energy, and through mitochondrial activity – or exogenous - through the release of substances like melatonin, the adoption of an appropriate diet, NIR-LED (Near Infra Red Light) – which stimulate the mitochondrial respiratory function, i.e., oxidative phosphorylation. The endogenous EI born and is formed in the mitochondria, the power plant of human body. The autopoietic system self-produces EI, by transforming EM – Energy Matter - including food, water and O2 - which is converted into EV-EI. Endogenously we produce ourselves the EV-EI indirectly with the breath, in the sense that vital energy is a subtle energy that occurs through breathing (it is not air, it is not breath, but it travels and is created together with it). Exogenously the EI is created by chemical transformations and biological properties of certain food we eat or through the release of specific substances (i.e., melatonin conjugated) or certain stimuli (i.e., NIR-LED) in order to improve the mitochondrial respiration. In biological systems the Energy-Information can be transmitted chemically - through metabolic processes - and / or electrically - with the neurotransmitters - peptides. The peptides can be imagined as "antenna", which carry information (waves) non-locally, simultaneously and synchronously by resonance (in case of non-local reality with high EI), or locally in space-time. In biological systems the EI is transmitted through the classic routes in the local reality, using substrates that reach the target tissue via blood, lymphatic, venous (hormones, cytokines, etc.) or through the nerve pathways (neurotransmitters) characterized by polarization - depolarization: there is time and energy consumption (if I move a substance from A to B, there is energy and time). On the contrary, in non-local reality pure and catalytic EI acts according to what is known in the microscopic world, expression of entanglement, observable with the QBS, of both worlds. DNA, like an antenna, simultaneously to "intense" stimulation on certain trigger - points, begins to "vibrate" catalyzing the reactions without energy expenditure, between the compound A and B, with production of C! For example: abdominal lateral pinch of fat "simultaneously" active function of liver PPAR (the mill that burns fat and glucose) revealed by the "simultaneous" local microcirculatory activation. There is a continuous structural coupling bodies-environment in all directions. If there is a tendency to disease (RR), the complex dynamics in biological system decreases: there is no chaos or lesser according to the fractal dimension (fD-fractal dimension), detectable through the reflex-diagnostic-percussio-auscultatory, with the simple use of the stethoscope, measuring the latency and duration of reflex. The absence of the strange attractor or of deterministic chaos is signal of low EI, the entropy is tending to zero, then in this case there is a local reality of information transmission – there is not the non-local reality. We must therefore enter EI (or create the conditions to increase it) in order to restore a sufficiently high level of EI. In accordance to angiobiopathy, improving mitochondrial activity in the parenchyma and in microvessel cells is involved favorably intracellular free energy and are improved various biological activities: the microcirculation will be normalized. QBS allows accurate and direct study of being and functioning of microvessels and only indirectly of the related parenchyma40. If it improves the way of being and functioning of the microcirculation it does mean that it is also improved the way of being and functioning of its parenchyma. This is done by stimulating the activity of mitochondria by acting on the vehicles that transmit EI: metabolism (chemical process), peptides' net (electric-electronic process), but also improving, normalizing tissue oxygenation, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy is the "sine qua non" of more frequent and severe human disease and not. Exogenous prevention and therapy (with environmental action) is done directly on EI – and related EV – at chemical level: proper diet,

conjugated melatonin, NIR-LED, or at electric level: such as acupuncture, which also acts on neurotransmitters or peptides. Endogenous prevention and therapy (autopoietic) can be implemented for example through: improving the quality of breath, improvement of lifestyles and rhythm styles and slow pace of the same (e.g. eating serene, calmly, as appropriate as possible) choice of appropriate physical activities (exercise, sports), yoga, meditation, prayer. We are a continuum of biological systems which interpenetrate and interact each others, and which in healthy conditions show a chaotic behavior, measured by the fractal dimension [1, 2, 3].

4. Conclusion

This article highlights the central role of mit-DNA in the process that underlies the degeneration of pancreatic cells. Mitochondrial function in dyslipidemia and diabetes explains why T2DM is a growing epidemic. Without enough energy, EI - Energy Information - associated with EV - Vibration Energy - originated by EM - Energy Matter (i.e., glucose, amino-acids, fats, etc.), the cell can not perform its normal functions. Under these conditions, therefore, the diseases arise under the action of the many negative environmental and acquired risk factors, which are not, however, to define the causes of diseases such as diabetes and cancer, since merely facilitators only for those at risk! In fact, in absence of 'Inherited Real Risk' of diabetes, based on CAEMH mitochondrial cytopathy, all factors achieved are innocent bystanders [18]. In conclusion, the doctor is now in a position to evaluate with a simple stethoscope the way of being and functioning of mitochondria, in any biological system of his patients, so that can provide appropriate, targeted and effective prevention and treatments. For this purpose, the new discipline of chaos theory with its invariant statistic measures, such as entropy and fractal dimension, plays a key role, both from theoretical and practical point of view. Today, the deterministic chaos emerges everywhere: in quantum physics, chemistry, biology, genetics, neuroscience, cognitive psychology, economics, art, cryptography, meteorology, even in the stock exchange. This article celebrates the importance of complexity theory in medicine, following a multidisciplinary approach where biology and quantum physics, chemistry and modern genetics, mathematics and genomics, are walking softly in harmony, penetrating each other, on its wake and assistance.

"In the human body and animal there is deterministic chaos that is not disorder, but a higher order type in physiology. Only in the pathology there is a lower order: the measure of the first order is an equilibrium called strange attractor, while the measure of the second one is called fixed point. In case of fixed point equilibrium the biological systems are linear, but when sufficient energy is introduced in them and they are properly stimulated, they show the characteristic behavior of nonlinear dynamical systems far from equilibrium (dissipative). Chaos requires enough energy to activate dissipative mechanisms, and life is the trajectory of an attractor: from strange attractor to fixed point, passing through the limit cycle. The main task of the doctor is to recognize promptly the various moments of the trajectory of the patient's life (in all and each of its biological systems), to intervene rapidly with appropriate therapy, useful and effective to reverse the dangerous direction of the trajectory toward irreversibility." Sergio Stagnaro

An example of this with incontrovertible evidence of the presence of deterministic chaos in the human body is given by clinical microangiology, where the universal constant of Feigenbaum (mark of chaos, comparable in importance to the Greek pi, the golden section and the constant number '*e*') always emerges as a relationship between lt and fD - fractal dimension (i.e., gastric aspecific reflex) in healthy subjects, while in the disease this measure states that the chaotic behavior disappears.

The precise evaluation of "central" adipose tissue microcirculation allows doctor to assess in an easy and rapid manner, clinically and on very large scale, the local function of MFR, and, therefore, starting from the first two individual's life decades, to recognize the dyslipidemic constitution, since genetically-dependent alterations involve contemporaneously both the parenchyma and respective microcircle. A lot of other biophysical-semeiotic evaluations, applicable by doctor skilled in the new physical semeiotics, allow to collect at the bed-side a large number of signs on microcirculation, which give information on local metabolic situation as well as on sensitivity of many receptors, e.g., insulin-receptors [12, 13]. A long clinical experience permits us to state that the knowledge of dyslipidemic constitution is of paramount importance in day-to-day practice and research: rapid, early, easy, "quantitative" bed-side recognising individuals at real risk of dyslipidemia is unavoidable to primary prevention of a serious disease, that can bring about well-known severe macro- and micro-vascular complications, i.e., morbidity and mortality. As regards the clinical research, the dyslipidemic constitution has allowed us to suggest an hypothesis, biophysical-semeiotic in nature, of type 2 diabetes mellitus, enlightening its natural history [16].

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